

Answer 1:

### Bibliographic Information

#### **Distribution and pharmacokinetics of the prodrug daunorubicin-GA3 in nude mice bearing human ovarian cancer xenografts.**

Houba, Pieter H. J.; Boven, Epie; van der Meulen-Muileman, Ida H.; Leenders, Ruben G. G.; Scheeren, Johannes W.; Pinedo, Herbert M.; Haisma, Hidde J. Department of Medical Oncology, University Hospital Vrije Universiteit, Amsterdam, Neth. *Biochemical Pharmacology* (1999), 57(6), 673-680. Publisher: Elsevier Science Inc., CODEN: BCPA6 ISSN: 0006-2952. Journal written in English. CAN 130:320339 AN 1999:124025 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

N-[4-daunorubicin-N-carbonyl (oxymethyl)phenyl] O- $\beta$ -glucuronyl carbamate (DNR-GA3) is a glucuronide prodrug of daunorubicin (DNR) which induced a better tumor growth delay than DNR when studied at equitoxic doses in three human ovarian cancer xenografts. These results suggested that the prodrug DNA-GA3 was selectively activated by human  $\beta$ -glucuronidase present in tumor tissue. We detd. the pharmacokinetics and distribution of DNR-GA3 in nude mice bearing human ovarian cancer xenografts (OVCAR-3, FMa, A2780, and MRI-H-207). Administration of DNR at 10 mg/kg i.v. (max. tolerated dose) to OVCAR-3-bearing mice resulted in a peak plasma concn. of the drug of 12.18  $\mu$ M ( $t = 1$  min). DNR-GA3 at 100 mg/kg i.v. (approx. 50% of the max. tolerated dose [MTD]) resulted in a peak plasma concn. of DNR that was 28-fold lower DNR concn. of DNR that was 28-fold lower than DNR itself; in normal prodrug injection resulted in 5- to 23-fold lower DNR concns. DNR showed a relatively poor uptake into OVCAR-3 tumors with a peak concn. of 2.05 nmol-g<sup>-1</sup> after injection. In the same xenograft, DNR-GA3 resulted in a significantly higher DNR peak concn. of 3.45 nmol-g<sup>-1</sup> ( $P < 0.05$ ). The higher area under the curve of DNR in tumor tissue after DNR-GA3 than after DNR itself would be the result of prodrug activation by  $\beta$ -glucuronidase. In this respect, a considerably higher  $\beta$ -glucuronidase activity was found in tumor tissue when compared to plasma. The specific activation of DNR-GA3 by  $\beta$ -glucuronidase at the tumor site relative to normal organs leads to a more tumor-selective therapy, resulting in greater efficacy without increased toxicity.

Answer 2:

### Bibliographic Information

#### **The use of daunomycin-antibody immunoconjugates in managing soft tissue sarcomas: nude mouse xenograft model.**

Stastny, Jaroslav J.; Das Gupta, Tapas K. Cancer Cent., Univ. Illinois, Chicago, IL, USA. *Cancer Research* (1993), 53(23), 5740-4. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 120:45402 AN 1994:45402 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Anal. of human fibrosarcoma cells exposed to radiolabeled monoclonal antibody 19-24, which recognizes sarcoma-assocd. antigen p102, revealed that over 54% of the cell surface-bound radioactivity was internalized. No modulation of cell surface p102 antigen by monoclonal antibody 19-24 was obsd. in human fibrosarcoma cells. Monoclonal antibody 19-24 coupled to daunomycin via a dextran bridge was found to be most effective. In different prepn.s., the daunomycin:total protein molar ratio ranged from 1.9 to 6.1. In vitro cytotoxicity studies using human fibrosarcoma cells showed that, at 10  $\mu$ g/mL concn., this immunoconjugate was 79.4% as efficient as free daunomycin and, at 1  $\mu$ g/mL concn., 36.8% as efficient. Control nonspecific murine monoclonal antibody P3 immunoconjugates were relatively ineffective. The distribution of <sup>14</sup>C-Adriamycin, <sup>125</sup>I-labeled monoclonal antibody 19-24, and <sup>125</sup>I-labeled 19-24 immunoconjugate was also evaluated over a 24-h period in tumor and normal tissues of athymic mice bearing a human fibrosarcoma xenograft. Poor uptake of radiolabeled Adriamycin by the tumor tissue was obsd. The level of <sup>14</sup>C radioactivity in the tumor tissue never exceeded 1% of the total injected dose and was 24.8-fold lower than the radioactivity found in the spleen tissue. Tumor tissue uptake of radiolabeled monoclonal antibody 19-24 was characterized by the high tumor tissue:blood ratio of 1.62. However, for monoclonal antibody 19-24 immunoconjugates, this ratio decreased to 0.66, which was still higher than normal (liver, 0.48; lung, 0.48; spleen, 0.28) or nonspecific monoclonal antibody P3 immunoconjugates (0.22). Thus, it appears that, compared to free daunomycin, monoclonal antibody 19-24 immunoconjugates may be more efficient and less cytotoxic to normal tissues.

Answer 3:

#### Bibliographic Information

**Comparative cytotoxic effect of anthracycline antibiotics on heterotransplants of human breast cancer cells cultivated in diffusion chambers in vivo.** Krutova, T. V.; Korman, D. B.; Batomunkueva, T. V. Inst. Khim. Fiz., Moscow, USSR. Antibiotiki i Khimioterapiya (1989), 34(11), 849-52. CODEN: ANKHEW ISSN: 0235-2990. Journal written in Russian. CAN 112:229409 AN 1990:229409 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The cytotoxic activity of doxorubicin, daunomycin, carminomycin, and ruboxyl against 50 human breast cancer heterotransplants was studied in diffusion chambers implanted in mice. The effect was estd. autoradiog. on the 6th or the 7th day of the cultivation after the drug administration in the max. tolerance doses. The tumors were considered sensitive when the labeling index of their transplants after the treatment was reduced by  $\geq 50\%$ . The no. of the tumors sensitive to all the drugs was 72-80%. Nineteen tumors were sensitive to 4 antibiotics. Fourteen and 8 tumors were sensitive to 3 and 2 antibiotics, resp., and only 1 tumor was sensitive to 1 drug. The sensitivity significantly correlated with the initial labeling index of the primary tumors and their heterotransplants. Thus, daunomycin and ruboxyl possessed a high cytotoxic activity close to that of doxorubicin and carminomycin and might be recommended for clin. trials in the treatment of patients with breast cancer.

Answer 4:

#### Bibliographic Information

**Chemotherapy with daunorubicin-anti-CEA conjugates in human colon adenocarcinoma grafted in nude mice.** Page, Michel; Delorme, Fernand; Lafontaine, Francine; Dumas, Louise. Fac. Med. Univ. Laval, Univ. Laval, QC, Can. Seminars in Oncology (1984), 11(4, Suppl. 3), 56-8. CODEN: SOLGAV ISSN: 0093-7754. Journal written in English. CAN 102:72517 AN 1985:72517 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

In nude mice with human colon adenocarcinoma xenografts, daunorubicin-anti-carcinoembryonic antigen conjugates limited tumor growth whereas treatment with either free daunorubicin or the antibody alone was not beneficial. The tumor cytotoxicity of the conjugate may be due to a concn. of the drug within the tumor and/or to a slower metab. of the drug.

Answer 5:

#### Bibliographic Information

**Screening test of antitumor agents by human tumor cell lines in nude mice in ascitic form.** Kitahara, Takeshi; Minato, Keisuke; Shimoyama, Masanori. Natl. Cancer Cent. Hosp., Japan. Gan no Rinsho (1984), 30(9), 1158-67. CODEN: GANRAE ISSN: 0021-4949. Journal written in Japanese. CAN 102:17008 AN 1985:17008 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Human breast cancer and leukemic cells implanted in nude mice appeared to be useful models for the screening of neoplasm inhibitors. The sensitivities of implanted tissues to drugs were similar to those found in patients. Studies on the suitable route of administration in these mice provide the best administration routes for humans.

Answer 6:

#### Bibliographic Information

**Subrenal capsule assay of human tumor chemosensitivity.** Konovalova N P; Diatchkovskaya R F; Ganieva L Kh; Volkova L M; Lapshin I M; Rudakov B Ya; Shaposhnikov Yu G; Shapiro A B Institute of Chemical Physics, USSR Academy of Sciences, Moscow Region Neoplasma (1991), 38(3), 275-84. Journal code: 0377266. ISSN:0028-2685. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1857448 AN 91312480 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### Abstract

Breast and colon tumor response to emoxyl, a nitroxyl derivative of daunomycin, was detected using human tumor heterotransplantation under the renal capsule of immunocompetent mice. The substitution of adriamycin by emoxyl in the combined therapy led to enhanced therapeutic efficacy. The evidence of enhanced response of breast tumors to emoxyl obtained during the histologic examination of xenografts is in good agreement with measurements of tumor fragment weight. It is suggested to use a quantitative kinetic index kappa calculated by the method of equivalent exponents for objective evaluation of tumor response to the drugs.

Answer 7:

#### Bibliographic Information

**Biodistribution and tumour localisation of a daunomycin-monoclonal antibody conjugate in nude mice with human tumour xenografts.** Pimm M V; Paul M A; Ogumuyiwa Y; Baldwin R W Cancer Research Campaign Laboratories, University of Nottingham, U.K Cancer immunology, immunotherapy : CII (1988), 27(3), 267-71. Journal code: 8605732. ISSN:0340-7004. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 3180150 AN 89028533 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### Abstract

The blood kinetics and tissue distribution of a conjugate of daunomycin and a monoclonal antibody (791T/36) have been examined in mice, including nude mice with human tumour xenografts reactive with the antibody. For this the antibody moiety of the conjugate was labelled with <sup>125</sup>I and the drug moiety assayed by radioimmunoassay. After radioiodination, the preparation had an immunoreactive fraction in isotopic binding tests with 791T cells of 74%. Both drug and antibody moieties were precipitable with anti-mouse Ig anti-serum. Following i.v. injection, blood clearance of the two components of the conjugate was essentially identical, and with the serum-borne conjugate both radiolabel and drug were co-precipitable. In mice with 791T xenografts, the tumour showed localisation of both drug and antibody moieties and at the time of analysis (3 days) tumour levels of drug were over 100 times those seen with free drug. In parallel studies with mice with antigen negative xenografts, there was no preferential localisation of antibody or drug moieties of the conjugate. These studies have shown in vivo stability of this conjugate, and site-specific targetting of an anti-tumour anthracycline.